# Rapid Assembly of the Salvileucalin B Norcaradiene Core

Sergiy Levin, Roger R. Nani, Sarah E. Reisman*

*The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125*

*reisman@caltech.edu*

## Supporting Information 1 (Experimental Procedures):

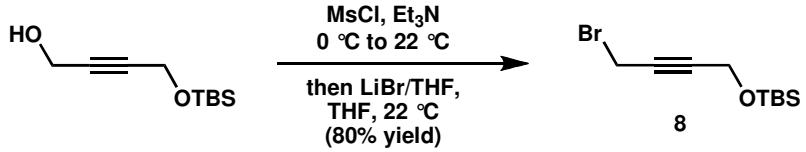
**General**. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride ($CH_2Cl_2$), diethyl ether ($Et_2O$), acetonitrile (MeCN), toluene and benzene were dried by passing through activated alumina columns. Dimethylformamide (DMF) was dried over activated molecular sieves, MeOH was distilled over magnesium oxide, dichloroethane (DCE) and triethyl amine ($Et_3N$) were distilled over calcium hydride. All other commercially obtained reagents were used as received unless specifically indicated. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash column chromatography was performed either as described by Still et al. (Still, W. C., Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.) using silica gel (partical size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Microwave experiments were performed using a Biotage Initiator® microwave reactor. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz respectively), and are reported relative to internal chloroform ($^1$H, $\delta$ = 7.26, $^{13}$C, $\delta$ = 77.0). Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption ($cm^{-1}$). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

**Catalyst abbreviations:**

| | |
|---|---|
| $Rh_2(OAc)_4$ | Rodium(II) acetate (Strem Chemicals) |
| $Rh_2(cap)_4$ | Rodium(II) capralactamate[1] |
| $Rh_2(tfa)_4$ | Rodium(II) trifluoroacetate (Strem Chemicals) |
| $Cu(acac)_2$ | Copper(II) acetylacetonate (Aldrich) |
| $Cu(tfacac)_2$ | Copper(II) trifluoroacetylacetonate (Strem Chemicals) |
| $Cu(hfacac)_2$ | Copper(II) hexafluoroacetylacetonate (Aldrich) |
| $Cu(TMHD)_2$ | Copper(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate) (Aldrich) |
| $Cu(TBS)_2$ | Copper(II) *tert*-butyl-*bis*-salicylimide[2] |
| $Pd(PPh_3)_4$ | Tetrakis(triphenylphosphine)Palladium(0) (Strem Chemicals) |
| RuCp*(cod)Cl | Chloro(1,5-cyclooctadiene)(pentamethylcyclopentadienyl) Ruthenium(II) (Strem Chemicals) |

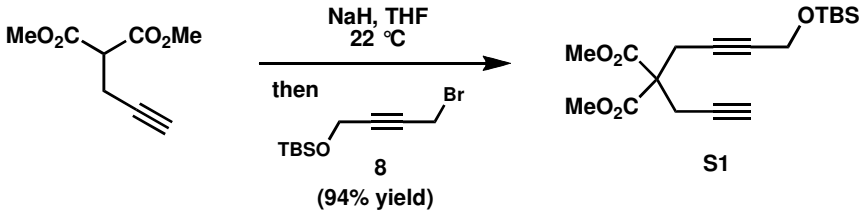
(1) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.
(2) Charles, R. G. *J. Org. Chem.* **1957**, *22*, 677.

**Preparation of Bromide 8**[3]




A 1 L flame-dried flask was charged with the mono-TBS protected diol (16.1 g, 80.4 mmol) under $N_2$, followed by THF (300 mL) and $Et_3N$ (20.5 mL, 147.0 mmol). The resulting solution was cooled to 0 °C in an ice bath, and MsCl (9.3 mL, 120 mmol) was added dropwise. The resulting thick white slurry was warmed to 22 °C over 30 min. In a separate flask, LiBr (35.0 g, 403 mmol) was charged under $N_2$ and dissolved in THF (250 mL). The mesylate/THF slurry was filtered directly into the clear yellow LiBr/THF solution at 22 °C. After 30 min TLC analysis indicated complete consumption of starting material. The reaction was diluted with $Et_2O$ (300 mL), filtered, and washed with brine (50 mL). The organic layer was dried ($Na_2SO_4$), concentrated, and purified by flash chromatography (10% EtOAc/hexanes) to afford bromide **8** (16.5 g, 80% yield) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) d 4.36 (t, $J$ = 2.1 Hz, 2H), 3.94 (t, $J$ = 2.1 Hz, 2H), 0.90 (s, 9H), 0.12 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 85.5, 79.7, 77.3, 76.8, 51.8, 25.8, 18.3, 14.5, -5.7; IR (NaCl/thin film): 2955, 2929, 2896, 2857 cm$^{-1}$; HRMS (EI+) calc'd for $C_{10}H_{19}OBrSi$ [M+] 264.0387, found 264.0368.

**Preparation of Diester S1**[4]

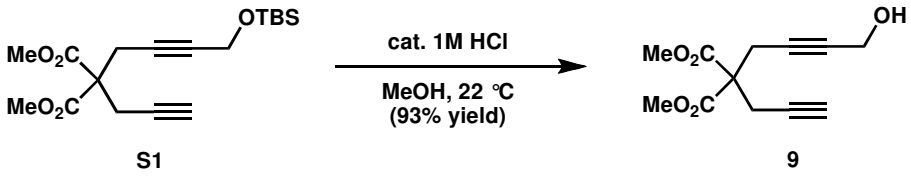



A 500 mL flame-dried flask was charged with NaH (1.3 g, 60% dispersion mineral oil, 32.5 mmol), followed by THF (150 mL) under $N_2$. The suspension was cooled to 0 °C in an ice bath, and propargyl dimethyl malonate (4.34 mL, 28.5 mmol) was added dropwise over 10 min. After stirring for 25 min (cessation of bubbling), bromide **8** (7.48 g, 28.4 mmol) in THF (100 mL) was added to the suspension at 0 °C. The reaction was warmed to 22 °C and stirred for 13 h, after which time TLC analysis indicated consumption of the starting materials. Water (300 mL)

(3) This compound has been reported previously, however the report contained limited experimental details and characterization data. See: Schore, N. E.; Najdi, S. D. *J. Org. Chem.* **1987**, *52*, 5296.
(4) Procedure was adapted from a known method: Trost, B.M.; Rudd, M.T. *J. Am. Chem. Soc.* **2003**, *125*, 12143.

was added, followed by extraction with $Et_2O$ (2 x 250 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield **S1** (9.27 g, 94% yield) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 4.22 (t, *J* = 2.1 Hz, 2H), 3.72 (s, 6H), 2.98 (t, *J* = 2.1 Hz, 2H), 2.93 (d, *J* = 2.7 Hz, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 0.86 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 169.0, 82.2, 78.8, 78.3, 77.3, 76.8, 71.6, 56.4, 53.0, 51.6, 25.7, 22.9, 22.6, 18.2, -5.3; IR (NaCl/thin film): 3292, 3001, 2956, 2931, 2897, 2858, 1744 cm$^{-1}$; HRMS (ES+) calc'd for $C_{18}H_{28}O_5Si$ $[M+H]^+$ 353.1779, found 353.1771.

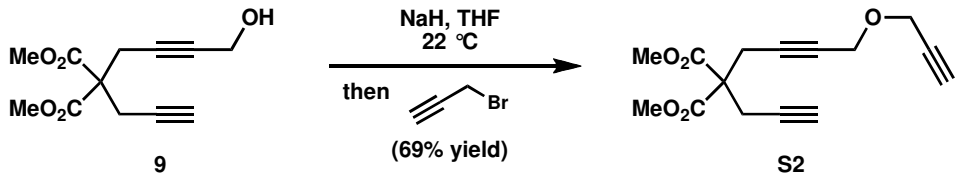
**Preparation of Alcohol 9**




**S1** **9**

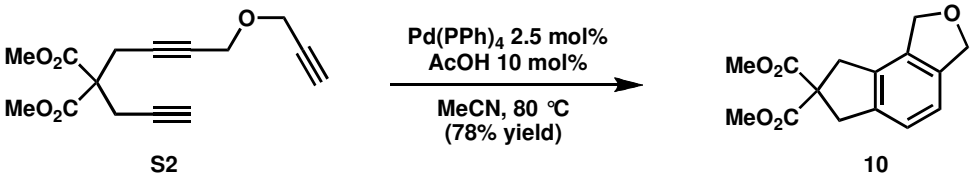
A 250 mL flask open to air was charged with **S1** (9.27 g, 26.3 mmol), followed by MeOH (80 mL) and aq. HCl (1M, 0.5 mL, 0.5 mmol) at 22 °C. The clear colorless solution was stirred for 3 h, then concentrated and purified by flash chromatography (0→20% MeOH/$CH_2Cl_2$), affording **9** (5.88 g, 93% yield) as light yellow oil. Characterization data is fully consistent with previous report.[4] $^1$H NMR (500 MHz, $CDCl_3$) δ 4.18 (dt, *J* = 6.1, 2.1 Hz, 2H), 3.74 (s, 6H), 2.99 (t, *J* = 2.0 Hz, 2H), 2.94 (d, *J* = 2.6 Hz, 2H), 2.23 (t, *J* = 6.2 Hz, 1H), 2.03 (t, *J* = 2.6 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 169.1, 82.0, 79.7, 78.2, 71.8, 56.4, 53.1, 50.9, 22.9, 22.7; IR (NaCl/thin film): 3483, 3288, 3008, 2957, 2871, 2848, 1739 cm$^{-1}$; HRMS (ES+) calc'd for $C_{12}H_{14}O_5$ $[M+H]^+$ 239.0914, found 239.0913.

**Preparation of Triyne S2**[5]




A 500 mL flame-dried flask was charged with NaH (1.09 g, 60% dispersion mineral oil, 27.3 mmol), followed by THF (100 mL) under $N_2$. In a separate flask **9** (5.88 g, 24.7 mmol) was dried by azeotrope with benzene (3X), and diluted with THF (75 mL). To the NaH/THF suspension pre-cooled to 0 °C, was added the solution of **9** via cannula. This brown mixture was stirred for 30 min at 0 °C, after which time propargyl bromide (80 wt% toluene, 3.20 mL, 28.7 mmol) was added in one portion. The resulting brown/black slurry was warmed to 22 °C and stirred for 22 h. After TLC analysis indicated consumption of the starting materials, water (500 mL) was added, and the reaction extracted with $Et_2O$ (2 x 250 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (0→25% EtOAc/hexanes) to afford **S2** (4.67 g, 69% yield) as an orange/brown oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 4.22 (t, *J* = 2.1 Hz, 2H), 4.21 (d, *J* = 2.4 Hz, 2H), 3.77 (s, 6H), 3.04 (t, *J* = 2.1 Hz, 2H), 2.98 (d, *J* = 2.6 Hz, 2H), 2.44 (t, *J* = 2.4 Hz, 1H), 2.03 (t, *J* = 2.7 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 169.1, 81.4, 78.9, 78.5, 78.3, 77.3, 76.8, 74.9, 71.8, 56.7, 56.5, 56.1, 53.2, 23.0, 22.8; IR (NaCl/thin film): 3286, 2955, 2916, 2850, 1738 cm$^{-1}$; HRMS (ES+) calc'd for $C_{15}H_{16}O_5$ $[M+H]^+$ 277.1071, found 277.1070.

**Preparation of Tricycle 10**[6]



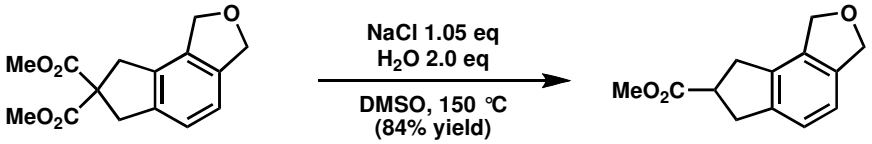

A 250 mL flask was charged with triyne **S2** (4.67 g, 16.9 mmol), followed by MeCN (150 mL) under $N_2$. Acetic acid (100 μL, 1.75 mmol) was added, followed by $Pd(PPh_3)_4$ (490

(5) This compound has been reported previously, however the report contained no experimental details or characterization data. See: Yamamoto, Y., Arakawa, T., Ogawa, R. and Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143.

(6) Negishi, E.; Harring, L.S.; Owczarczyk, Z.; Mohamud, M.M.; Ay, M. *Tetrahedron Lett.* **1992**, *33,* 3243.

mg, 0.424 mmol) in one portion at 22 °C. The flask was fitted with a condenser, and the clear orange/red solution was heated to 80 °C. After 30 min the reaction was complete (TLC analysis) and subsequently cooled to 22 °C. The solvent was removed via rotary evaporation, and the crude oil was purified by flash chromatography (0→25% EtOAc/hexanes) to afford **10** (3.65 g, 78% yield) as a white solid. Characterization data is fully consistent with previous report.[5] $^1$H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 5.08 (s, 2H), 5.04 (s, 2H), 3.75 (s, 6H), 3.61 (s, 2H), 3.49 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.9, 139.3, 138.2, 134.9, 132.9, 123.1, 119.5, 73.6, 72.4, 60.6, 53.0, 40.2, 38.9; IR (NaCl/thin film): 3436, 3003, 2954, 2916, 2850, 1733 cm$^{-1}$; HRMS (ES+) calc'd for $C_{15}H_{16}O_5$ [M-H]+ 275.0925, found 275.0917.

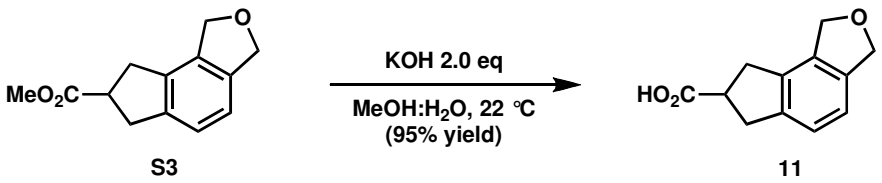
**Preparation of Tricycle S3**




**10** **S3**

A 250 mL flask open to air was charged with diester **10** (6.43 g, 23.3 mmol), NaCl (1.44 g, 24.6 mmol), water (840 μL, 46.6 mmol) and DMSO (65 mL) at 22 °C. The flask was fitted with a reflux condenser and heated to 150 °C with vigorous stirring. Upon heating, the reaction darkened from light yellow to brown, and after 30 min at 150 °C was black. After heating for 12 h TLC analysis indicated consumption of starting material, and the reaction was cooled to 22 °C. The reaction was diluted with hexanes/$Et_2O$ (700 mL, 7:3) and washed with water (2 x 300 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (0→30% EtOAc/hexanes) to afford **S3** (4.2 g, 84% yield) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.10 (s, 2H), 5.04 (s, 2H), 3.43 – 3.35 (tt, *J* = 9.0, 8.0 1H), 3.30 – 3.20 (m, 2H), 3.16 (dd, *J* = 16.1, 7.7 Hz, 1H), 3.09 (dd, *J* = 16.1, 9.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.5, 141.0, 137.8, 135.0, 134.6, 123.2, 119.1, 73.7, 72.5, 52.0, 43.7, 35.8, 34.4; IR (NaCl/thin film): 3468, 3022, 2948, 2848, 1729 cm$^{-1}$; HRMS (ES+) calc'd for $C_{13}H_{14}O_3$ $[M-H]^+$ 217.0870, found 217.0859.

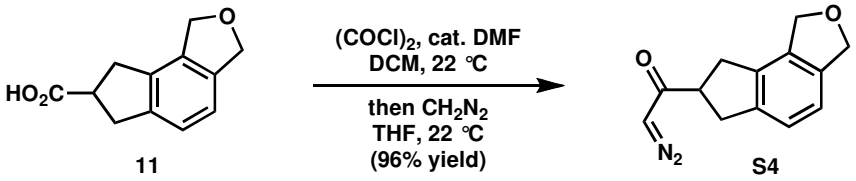
**Preparation of Carboxylic Acid 11**




S3 11

A 250 mL flask open to air was charged with monoester **S3** (4.50 g, 20.6 mmol), MeOH (100 mL), water (10 mL), and KOH (2.30 g, 41.0 mmol) at 22 °C. After 4.5 h the reaction was judged complete by TLC, and the reaction volume was reduced to approximately 50 mL total via rotary evaporation. The carboxylate solution was diluted with $Et_2O$ (150 mL) and washed with 1M HCl. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, yielding **11** (4.0 g, 95% yield) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 3.48 – 3.40 (tt, *J* = 9.0, 7.5 Hz, 1H), 3.34 – 3.23 (m, 2H), 3.20 (dd, *J* = 16.2, 7.4 Hz, 1H), 3.13 (dd, *J* = 16.1, 9.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 180.90, 140.85, 137.69, 134.88, 134.39, 123.27, 119.22, 73.62, 72.44, 43.51, 35.60, 34.20; IR (NaCl/thin film): 3436, 3152, 2998, 2948, 2867, 2746, 2638, 1726 cm$^{-1}$; HRMS (ES+) calc'd for $C_{12}H_{11}O_3$ $[M-H]^+$ 203.0714, found 203.0703.

**Preparation of Diazo Ketone S4**

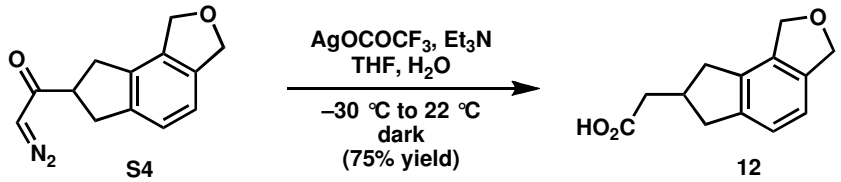



11 S4

A flame-dried 250 mL flask containing acid **11** (3.00 g, 14.7 mmol) was charged with $CH_2Cl_2$ (100 mL) under $N_2$. To the resulting slurry was added 1 drop of DMF, followed by oxalyl chloride (2.33 mL, 27.5 mmol) at 22 °C. Within 15 min the solids dissolved, yielding a clear brown solution. After 2 h the $CH_2Cl2_2$ was removed under reduced pressure, and the residue was dried by azeotrope with anhydrous benzene (2 x 50 mL). $^1$H NMR analysis of an aliquot confirmed clean conversion of the starting acid **11** to the acid chloride. The resulting murky brown oil was diluted with THF (100 mL) under $N_2$. Diazomethane (~50-60 mmol, solution in $Et_2O$) was briefly dried over KOH (5 min) and carefully decanted at 0 °C into a 500 mL Erlenmeyer flask. The acid chloride/THF solution was then carefully transferred via cannula to excess diazomethane at 0 °C with gentle stirring, resulting in steady gas evolution. After 30 min the starting material was completely consumed (TLC analysis), and the reaction was concentrated under reduced pressure. The crude brown oil was purified by flash chromatography

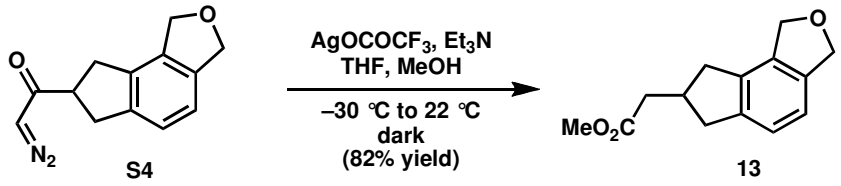
(0→40% EtOAc/hexanes), yielding diazo ketone **S4** (3.0 g, 96% yield) as a yellow solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.31 (bs, 1H), 5.09 (s, 2H), 5.04 (s, 2H), 3.37 (m, 1H), 3.27 – 3.10 (m, 3H), 3.03 (dd, *J* = 16.1, 8.9 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 196.00, 140.89, 137.87, 135.05, 134.53, 123.24, 119.21, 73.67, 72.49, 53.97 (br), 49.64 (br), 35.74, 34.22; IR (NaCl/thin film): 3496, 3081, 3027, 2938, 2900, 2849, 2104, 1635 cm$^{-1}$; HRMS (ES+) calc'd for $C_{13}H_{12}N_2O_2$ $[M+H]^+$ 229.0972, found 229.0973.

**Preparation of Carboxylic Acid 12**



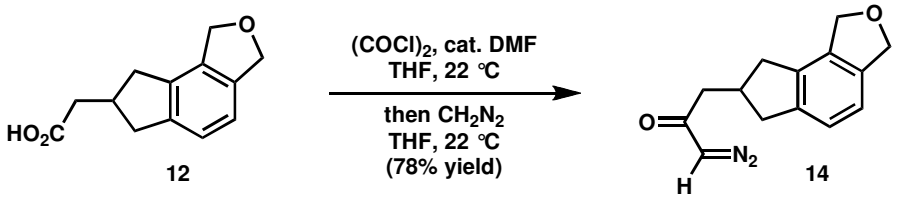

A 250 mL flask was charged with diazo ketone **S4** (3.00 g, 13.1 mmol), THF (55 mL), and water (5.5 mL), then purged with $N_2$. The flask was covered in foil and cooled to –30 °C. To a 5 mL conical flask under an $N_2$ atmosphere and protected from light was added silver trifluoroacetate (290 mg, 1.31 mmol), followed by $Et_3N$ (5.50 mL, 49.5 mmol) with vigorous stirring at 22 °C. (Note: vigorous stirring during $Et_3N$ addition is critical to ensure dissolution of silver salt. Lack of stirring can result in a brown silver clump and incomplete dissolution. When dissolved one obtains a clear tan solution). The $Et_3N$/Ag solution was added in one portion to the clear yellow diazo ketone solution at –30 °C. The reaction was slowly warmed over 4 h (starting material consumed by TLC), after which the reaction was quenched with 1M HCl (300 mL). The product was extracted with $Et_2O$ (2 x 250 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The brown solid was purified by silica gel chromatography (0→50% EtOAc/hexanes), affording **12** (2.16 g, 75% yield) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 6.8 Hz, 1H), 5.11 (s, 2H), 5.07 – 5.00 (m, 2H), 3.19 (dd, *J* = 15.6, 7.9 Hz, 1H), 3.07 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.95 (septet, *J* = 7.5 Hz, 1H), 2.69 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.64 – 2.43 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.1, 142.0, 137.4, 135.5, 135.1, 123.4, 118.9, 73.7, 72.6, 39.6, 38.5, 37.1, 36.1; IR (NaCl/thin film): 3026, 2935, 2848, 2909, 2680, 1728, 1706 cm$^{-1}$; HRMS (ES+) calc'd for $C_{13}H_{13}O_3$ $[M–H]^–$ 217.0865, found 217.0872.

**Preparation of Ester 13**




A 50 mL flame-dried flask was charged with diazo ketone **S4** (107 mg, 0.470 mmol), THF (5 mL), and MeOH (500 μL), then was purged with $N_2$. The flask was covered in foil and cooled to –30 °C. To a 5 mL conical flask under an $N_2$ atmosphere and protected from light was added silver trifluoroacetate (10 mg, 0.045 mmol), followed by $Et_3N$ (196 μL, 1.41 mmol) with vigorous stirring at 22 °C. (Note: vigorous stirring during $Et_3N$ addition is critical to ensure dissolution of silver salt. Lack of stirring can result in a brown silver clump and incomplete dissolution. When dissolved one obtains a clear tan solution). The $Et_3N$/Ag solution was added in one portion to the clear yellow diazo ketone solution at –30 °C. The reaction was slowly warmed over 4 h (starting material consumed by TLC), after which time became was a clear red/brown solution. The reaction was quenched with 1M HCl (1 mL), and diluted with $Et_2O$ (50 mL). The aqueous layer was extracted with $Et_2O$ (20 mL), and the combined organics were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude brown oil was purified by silica gel chromatography (0→25% EtOAc/hexanes), yielding **13** (89 mg, 82% yield) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 5.10 (m, 2H), 5.07 – 4.98 (m, 2H), 3.70 (s, 3H), 3.16 (dd, *J* = 15.6, 7.9 Hz, 1H), 3.04 (dd, *J* = 15.7, 7.9 Hz, 1H), 2.95 (septet, *J* = 7.5 Hz, 1H), 2.65 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.57 – 2.47 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.2, 142.0, 137.4, 135.6, 135.0, 123.3, 118.7, 73.6, 72.5, 51.5, 39.7, 38.5, 37.1, 36.3; IR (NaCl/thin film): 3470, 3020, 2949, 2903, 2845, 1736 cm$^{-1}$; HRMS (FAB+) calc'd for $C_{14}H_{15}O_3$ [M+H]-$H_2$ 231.1025, found 231.1021.

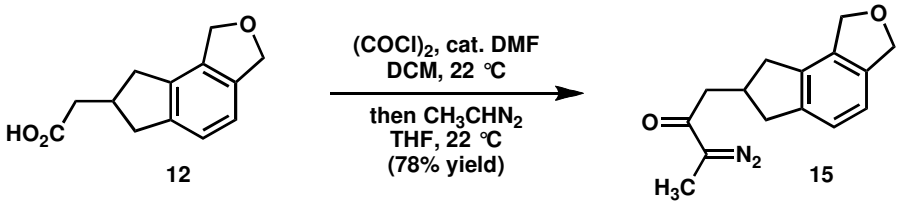
**Preparation of Diazo Ketone 14**




A flame-dried 50 mL flask containing acid **12** (154 mg, 0.706 mmol) was charged with THF (10 mL) under $N_2$. To the solution was added 1 drop of DMF, followed by oxalyl chloride (120 μL, 1.42 mmol) at 22 °C. After gas evolution had ceased (20 min), the dark yellow solution

was concentrated under reduced pressure and azeotroped with benzene (3 x 10 mL). $^1$H NMR analysis of an aliquot confirmed clean conversion of the starting acid **12** to the acid chloride. The resulting murky brown oil was diluted with THF (20 mL) under $N_2$. Diazomethane (15 mL, ~0.4M solution in $Et_2O$) was briefly dried over KOH (5 min) and carefully decanted at 0 °C into a 100 mL flask under $N_2$. The solution of the acid chloride in THF was then carefully transferred via cannula over 5 min to the diazomethane at 0 °C with gentle stirring, resulting in steady gas evolution. After 30 min the starting material was completely consumed (TLC analysis), and the concentrated under reduced pressure. The crude yellow oil was purified by flash chromatography (0→40% EtOAc/hexanes), yielding diazo ketone **14** (125 mg, 78% yield) as a yellow solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 5.26 (bs, 1H), 5.09 (s, 2H), 5.06 – 4.98 (m, 2H), 3.15 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.07 – 2.92 (m, 2H), 2.64 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.57 – 2.45 (m, 3H). IR (NaCl/thin film): 3082, 2933, 2890, 2845, 2010, 1637 $cm^{-1}$; HRMS (ES+) calc'd for $C_{14}H_{14}N_2O_2$ $[M+H]^+$ 243.1128, found 243.1125.

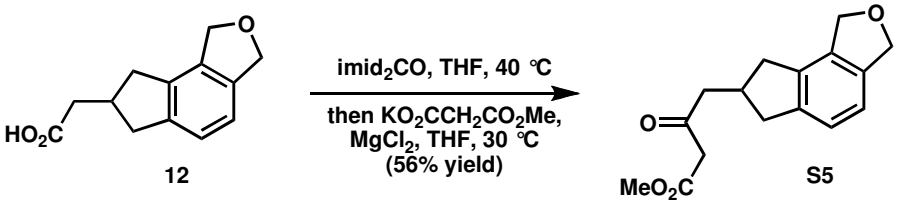
**Preparation of Diazo Ketone 15**




A flame-dried 50 mL flask containing acid **12** (97 mg, 0.44 mmol) was charged with $CH_2Cl_2$ (5 mL) under $N_2$. To this solution was added 1 drop of DMF, followed by oxalyl chloride (74 μL, 0.88 mmol) at 22 °C. After 1 hour the reaction mixture was concentrated under reduced pressure. $^1$H NMR analysis confirmed clean conversion of the starting acid **12** to the acid chloride. The resulting murky brown oil was diluted with THF (9 mL) under $N_2$, and cannulated into a freshly prepared ethereal diazoethane solution (20 mL, ~ 10 mmol) at 0 °C. The reaction mixture was warmed to 22 °C over 12 h. The reaction mixture was concentrated under reduced pressure (with acetic acid in the trap to quench any unreacted diazoethane). The crude dark yellow oil was purified by flash chromatography (0→50% EtOAc/hexanes), yielding diazo ketone **15** (70 mg, 63% yield) as a yellow solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.09 (s, 2H), 5.01 (s, 2H), 3.16 (dd, *J* = 15.5, 7.4 Hz, 1H), 3.10 – 2.89 (m, 2H), 2.72 – 2.57 (m, 2H), 2.51 (dd, = 15.1, 6.0 Hz, 1H), 2.17 – 2.04 (br. s, 1H* methyl rotamer), 2.00 – 1.92 (br. s, 2H* methyl rotamer); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 193.5, 142.0, 137.4, 135.6, 135.1, 123.3, 118.7, 73.6, 72.5, 62.5, 43.1, 38.6, 37.1, 36.2, 8.0. IR (NaCl/thin film): 2916, 2848, 2068, 1631 cm$^{-1}$; HRMS (ES+) calc'd for $C_{15}H_{17}N_2O_2$ $[M+H]^+$ 257.1290, found 257.1284.

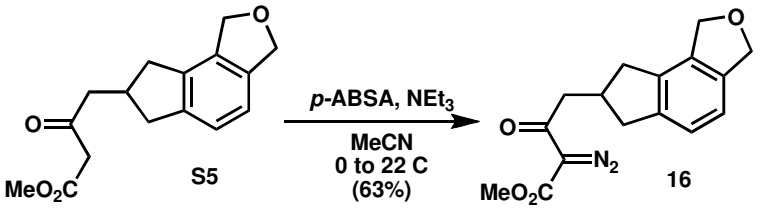
Preparation of diazoethane: *N*-ethyl-*N*-nitrosourea (1.7 g, 15 mmol) in diethyl ether (20 mL) was slowly added to a stirred 60% aqueous KOH solution (20 mL) at 0 °C. When gas evolution ceased (15 min), the ethereal layer was separated and briefly dried with KOH (5 min) at 0 °C. **Warning**: Diazoethane is a highly toxic volatile compound.

**Preparation of β-Ketoester S5**



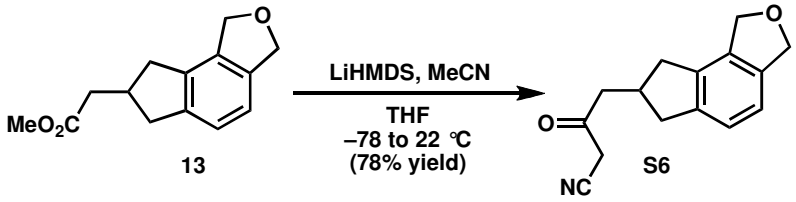

A flame-dried 25 mL round-bottom flask equipped with stir bar and reflux condenser was charged with potassium monomethyl malonate (156 mg, 1.00 mmol) and $MgCl_2$ (70 mg, 0.74 mmol). This flask was evacuated and backfilled with nitrogen 3 times. THF (2 mL) was added and the suspension was heated to 65 °C for 3 h, followed by 30 °C for 2 h. A separate 15 mL flame-dried round-bottom flask was charged with acid **12** (160 mg, 0.73 mmol) in THF (1 mL) and carbonyl diimidazole (140 mg, 0.88 mmol) was added as a suspension in THF (2 mL). The flask was fitted with a reflux condenser and the solution was heated at 40 °C for 1 hour. The resulting acyl imidazole solution was added dropwise via syringe to the magnesium malonate suspension at 30 °C (NOTE: a white precipitate forms rapidly, and vigorous stirring is necessary to avoid clumping). After 40 h the white suspension was cooled to 0 °C and quenched by the addition of 1M HCl (5 mL). The reaction was extracted into EtOAc (3 x 10 mL), washed with water (ca. 15 mL), saturated aqueous NaCl (ca. 15 mL), dried over anhydrous $Na_2SO_4$, and filtered. Concentration under reduced pressure yielded a crude oil, which was purified by flash chromatography (0→40% EtOAc/hexanes), yielding β-ketoester **S5** (113 mg, 56% yield) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$, compound exists as a 10:1 mixture of ketone : enole tautomers, only major ketone peaks are reported) δ 7.10 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.09 (apparent s, 2H), 5.07 – 4.93 (m, 2H), 3.75 (s, 1H), 3.47 (s, 2H), 3.17 (dd, *J* = 15.7, 7.9 Hz, 1H), 3.06 (dd, *J* = 15.7, 7.9 Hz, 1H), 3.02 – 2.92 (m, 1H), 2.82 – 2.73 (m, 2H), 2.58 (dd, *J* = 15.6, 7.1 Hz, 1H), 2.46 (dd, *J* = 15.7, 6.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$ compound exists as a 10:1 mixture of ketone : enol tautomers, ketone tautomer is designated by $^*$, enol tautomer is denoted by $^§$) δ $^{13}$C NMR (125 MHz, $CDCl_3$) δ 201.9*, 177.3$^§$, 172.9$^§$, 167.5*, 142.1$^§$, 142.0$^*$, 137.41*, 137.38$^§$, 135.6$^§$, 135.5*, 135.1*, 123.3*, 118.8*, 89.7$^§$, 73.7*, 72.5*, 52.4*, 51.1$^§$, 49.2*, 48.7*, 40.7$^§$, 38.5*, 38.4$^§$, 37.2$^§$, 37.1*, 36.9$^§$, 34.9*. IR (NaCl/thin film): 2840, 1744, 1712 cm$^{-1}$; HRMS (ES+) calc'd for $C_{16}H_{17}O_4$ $[M+H]^+$ 275.1283, found 275.1266.

**Preparation of Diazo β-Ketoester 16**




To a flame-dried 15 mL round-bottom flask was added β-ketoester **S5** (160 mg, 0.58 mmol), *p*-ABSA (182 mg, 0.76 mmol) and dry MeCN (5 mL). The reaction mixture was cooled to 0 °C and triethylamine (180 μL, 1.3 mmol) was added in one portion. The reaction mixture was allowed to warm up to 22 °C over the period of 12 h, after which time TLC analysis showed complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure and treated with 3:1 pentane:EtOAc (ca 10 mL). The slurry was filtered and the filtrate was concentrated under vacuum. The crude white solid was purified by flash chromatography (3:1 pentane:EtOAc) yielding diazoketone **16** (110 mg, 63% yield) as a white solid. NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 5.09 (s, 2H), 5.02 (apparent s, 2H), 3.83 (s, 3H), 3.16 (dd, *J* = 15.5, 7.4 Hz, 1H), 3.09 – 3.05 (m, 2H), 3.04 – 2.96 (m, 2H), 2.66 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.53 (dd, *J* = 15.3, 6.3 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 191.9, 161.7, 142.2, 137.25, 135.8, 135.0, 123.3, 118.6, 76.0, 73.7, 72.5, 52.2, 45.8, 38.6, 37.1, 35.8. IR (NaCl/thin film): 2953, 2900, 2846, 2135, 1722, 1655 $cm^{-1}$; HRMS (ES+) calc'd for $C_{16}H_{15}N_2O_4$ $[M–H]^-$ 299.1037, found 299.1028.

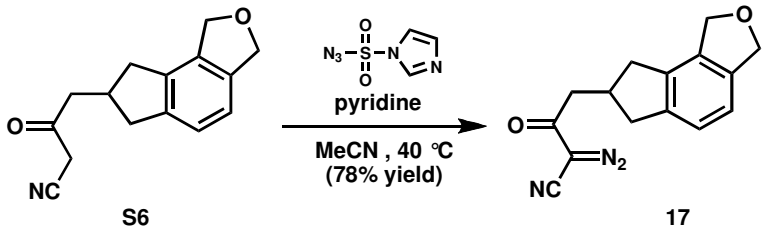
**Preparation of β-Ketonitrile S6**




A flame-dried 25 mL round-bottom flask was charged with LiHMDS (1M solution in THF, 750 μL, 0.75 mmol) and THF (2 mL), and cooled to –78 °C. MeCN (45 μL, 0.86 mmol) was added dropwise and solution was stirred at –78 °C for 30 min. A solution of ester **13** (83 mg, 0.36 mmol) in THF (5 mL) was added dropwise and resulting solution was stirred at –78 °C for 30 min and subsequently warmed to 22 °C. TLC analysis showed complete consumption of starting material. $Et_2O$ (20 mL) was added and reaction was quenched by the addition of aqueous saturated $NH_4Cl$ (3 mL). The organic layer was washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude yellow oil was purified

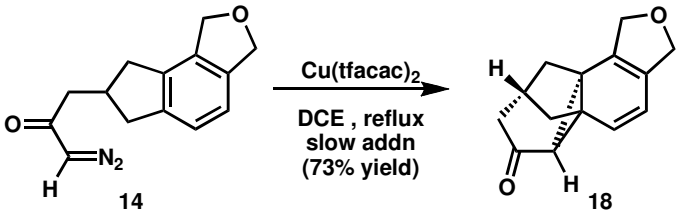
by flash chromatography (0→40% EtOAc/hexanes) to yield β-ketonitrile **S6** (79 mg, 91% yield) as a yellow oil. NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.09 (appar. s, 2H), 5.06 – 4.93 (m, 2H), 3.47 (s, 2H), 3.19 (dd, *J* = 15.7, 7.8 Hz, 1H), 3.08 (dd, *J* = 15.8, 7.9 Hz, 1H), 3.03 – 2.91 (m, 1H), 2.91 – 2.77 (m, 2H), 2.59 (dd, *J* = 15.7, 6.9 Hz, 1H), 2.47 (dd, *J* = 15.8, 6.7 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 196.8, 141.5, 137.5, 135.1, 135.1, 123.3, 118.9, 113.7, 73.6, 72.4, 47.7, 38.3, 36.9, 34.7, 32.2. IR (NaCl/thin film): 2943, 2911, 2847, 2260, 1730 $cm^{-1}$; HRMS (ES+) calc'd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1181, found 242.1176.

**Preparation of Diazo β-Ketonitrile 17**




Pyridine (1.13 mL, 14.0 mmol) was added to a solution of imidazole-1-sulfonyl azide[7] (581 mg, 3.36 mmol) and β-ketonitrile **S6** (675 mg, 2.80 mmol) in MeCN (25 mL). Reaction mixture was stirred at 40 °C for 7 h, after which time TLC analysis confirmed consumption of the starting β-ketonitrile **S6**. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by flash chromatography (0→50% EtOAc/hexanes), yielding diazo β-ketonitrile **17** (460 mg, 62% yield) as a white solid. NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.08 (s, 2H), 5.01 (s, 2H), 3.18 (dd, *J* = 15.6, 7.5 Hz, 1H), 3.13 – 2.92 (m, 2H), 2.92 – 2.74 (m, 2H), 2.66 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.54 (dd, *J* = 15.1, 6.1 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 189.3, 141.5, 137.6, 135.12, 135.07, 123.4, 119.0, 108.3, 73.7, 72.5, 57.5, 44.9, 38.4, 37.0, 35.8. IR (NaCl/thin film): 2896, 2847, 2222, 2129, 1674 $cm^{-1}$; HRMS (ES+) calc'd for $C_{15}H_{14}NO_2$ $[M–N_2+H]^+$ 240.1019, found 240.1016.

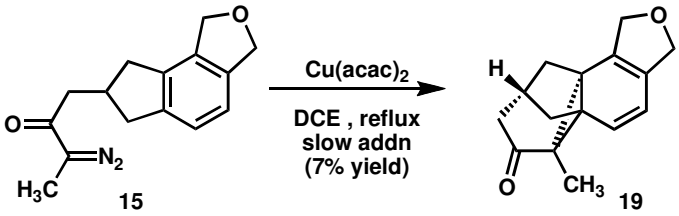
**Cyclopropanation of Diazoketone 14**




(7) Goddard-Borger, E. D; Stick, R. V. *Org. Lett.* **2007**, 9, 3797-3800.

A flame-dried 250 mL three-neck round bottom flask, equipped with stir bar, water-cooled condenser and septa, was charged with a solution of $Cu(tfacac)_2$ (54 mg, 0.15 mmol) in DCE (20 mL) and was heated to reflux under nitrogen. After 15 min a solution of **14** (0.70 g, 2.9 mmol) in DCE (40 mL) was added at the rate of 0.8 mL/min (syringe pump). Upon completion of the addition, heating was continued for an additional 20 min. TLC analysis confirmed consumption of the starting diazoketone **14**, and reaction mixture was concentrated under reduced pressure. The crude brown oil was purified by flash chromatography (0→40% EtOAc/hexanes), yielding norcaradiene **18** (450 mg, 73% yield) as yellow oil, which slowly turns into yellow solid upon storage at -20 °C. NMR (500 MHz, $CDCl_3$) δ 6.27 (d, *J* = 9.4 Hz, 1H), 6.01 (d, *J* = 9.4 Hz, 1H), 5.05 – 4.85 (m, 1H), 4.85 – 4.58 (m, 3H), 2.35 – 2.25 (m, 1H), 2.18 (d, *J* = 3.0 Hz, 2H), 2.08 – 2.00 (m, 2H), 1.99 (dd, *J* = 12.2, 5.2 Hz, 1H), 1.94 (d, *J* = 12.1 Hz, 1H), 1.05 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 209.1, 133.3, 129.4, 128.1, 118.4, 75.2, 75.1, 43.8, 43.2, 39.2, 38.2, 35.6, 34.0, 27.4. IR (NaCl/thin film): 2932, 2863, 1690, $cm^{-1}$; HRMS (ES+) calc'd for $C_{14}H_{15}O_2$ $[M+H]^+$ 215.1072, found 215.1068.

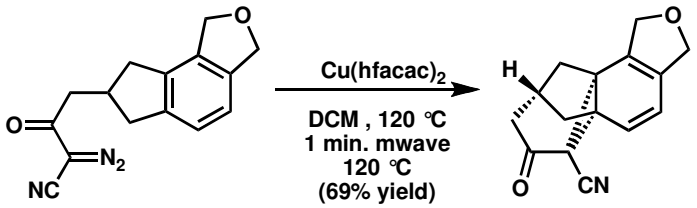
**Cyclopropanation of Diazoketone 15**




A flame-dried 50 mL three-neck round bottom flask, equipped with stir bar, water-cooled condenser and septa, was charged with the solution of $Cu(acac)_2$ (2.6 mg, 0.01 mmol) in DCE (10 mL) and was heated to reflux under nitrogen. After 10 min, a solution of **15** (50 mg, 0.20 mmol) in DCE (20 mL) was added at a rate of 10 mL/hour (syringe pump). Upon completion of the addition, the solution was heated at reflux for additional 60 min. TLC analysis confirmed consumption of the starting diazoketone **15**, and reaction mixture was concentrated under reduced pressure. The crude brown oil was purified by preparative HPLC chromatography (20→50% EtOAc/hexanes), yielding norcaradiene **19** (3 mg, 7% yield) as white solid. NMR (500 MHz, $CDCl_3$) δ δ 6.16 (d, *J* = 9.4 Hz, 1H), 6.04 (d, *J* = 9.5 Hz, 1H), 4.91 – 4.59 (m, 4H), 2.27 – 2.25 (m, 2H), 2.25 – 2.18 (m, 1H), 2.07 – 2.00 (m, 2H), 1.98 – 1.94 (m, 2H), 0.75 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 209.1, 131.59, 131.54, 126.5, 120.6, 75.4, 75.0, 46.6, 45.0, 40.5,

36.9, 35.2, 31.1, 26.7, 7.0. IR (NaCl/thin film): 2927, 2850, 1738 (weak) 1682, $cm^{-1}$ HRMS (ES+) calc'd for $C_{15}H_{17}O_2$ $[M+H]^+$ 229.1229, found 229.1223.

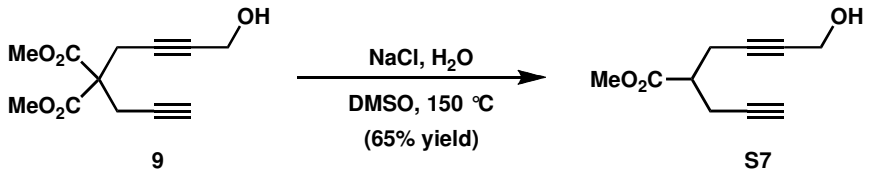
**Cyclopropanation of Diazo β-Ketonitrile 17**




17 21

A microwave reaction vessel equipped with a stir bar was charged with a solution of diazo β-ketonitrile **17** (53 mg, 0.2 mmol) in $CH_2Cl_2$ (10 mL). $Cu(hfacac)_2$ (9.5 mg, 0.02 mmol) in $CH_2Cl_2$ (2 mL) was added via syringe through the septa of the sealed vial. The vial was placed in the microwave reactor and heated to 120 °C for 1 minute (ramp from 22 °C to 120 °C required 2 min). TLC analysis confirmed consumption of the starting material. The solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography (0→100% EtOAc/hexanes), yielding norcaradiene **21** (30 mg, 64% yield) as a white solid. $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.41 (d, *J* = 9.5 Hz, 1H), 6.27 (d, *J* = 9.5 Hz, 1H), 5.02 – 4.84 (m, 2H), 4.84 – 4.69 (m, 2H), 2.46 – 2.40 (m, 1H), 2.39 – 2.30 (m, 2H), 2.24 – 2.15 (m, 3H), 2.11 (d, *J* = 12.7 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 199.0, 134.7, 130.0, 124.4, 123.0, 111.8, 75.0, 74.6, 51.1, 47.0, 43.4, 36.0, 34.6, 29.7, 26.3. IR (NaCl/thin film): 2963, 2850, 2234, 1691, $cm^{-1}$; HRMS (ES+) calc'd for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1019, found 240.1025.

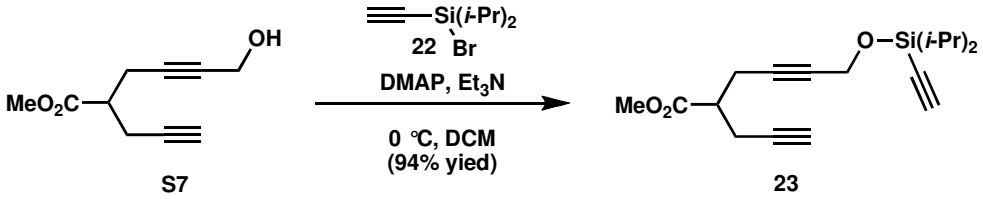
**Preparation of S8**




9 S7

A 250 mL flask open to air was charged with diester **9** (4.95 g, 20.8 mmol), NaCl (1.30 g, 22.3 mmol), water (740 μL, 41.1 mmol) and DMSO (80 mL). The flask was fitted with a condenser and heated to 150 °C with vigorous stirring. Upon heating, the reaction darkened from light yellow to brown, and after 30 min at 150 °C was black. After heating for 11 h TLC analysis indicated consumption of the starting material, and reaction was cooled to 22 °C. The reaction was diluted with $CH_2Cl_2$ (500 mL) and washed with aqueous NaCl (2 x 250 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (0→80% EtOAc/hexanes) to afford **S8** (2.44 g, 65% yield) as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 4.24 (dt, *J* = 6.1, 2.1 Hz, 2H), 3.74 (s, 3H), 2.76 (tt, *J* = 7.1, 5.9 Hz, 1H), 2.70 – 2.65 (m, 2H), 2.65 – 2.53 (m, 2H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.48 (t, *J* = 6.1 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.0, 81.5, 80.7, 80.3, 70.5, 52.1, 50.7, 42.9, 42.8, 20.1, 20.0, 19.8, 19.7. IR (NaCl/thin film): 3292, 2953, 2916, 1727. HRMS (FAB) calc'd for $C_{10}H_{13}O_3$ $[M+H]^+$ 181.0865, found 181.0860.

**Preparation of Triyne 23**



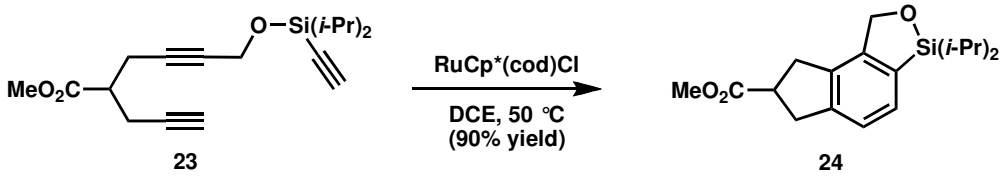

S7 23

A freshly prepared solution of bromo(ethynyldiisopropyl)silane **22**[8] (17.3 mmol) in $CH_2Cl_2$ (100 mL) was slowly added to a solution of alcohol **S7** (2.44 g, 13.5 mmol), triethylamine (3.80 mL, 27.3 mmol) and DMAP (330 mg, 2.7 mmol) in $CH_2Cl_2$ (50 mL) at 0 °C. The reaction mixture was allowed to warm up to 22 °C over a period of 24 h. The solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography (0→40% EtOAc/hexanes), yielding triyne **23** (4.03 g, 94% yield) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 4.42 (t, *J* = 2.1 Hz, 2H), 3.73 (s, 3H), 2.80 – 2.70 (m, 1H), 2.70 – 2.56 (m,

(8) Petit, M.; Chouraqui, G.; Aubert, C.; Malacria, M. *Org. Lett*. **2003**, 5, 2037.

4H), 2.47 (s, 1H), 2.00 (t, $J$ = 2.1 Hz, 1H), 1.12 – 0.96 (m, 14H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.9, 95.5, 83.8, 81.5, 80.6, 80.4, 70.4, 53.0, 52.1, 43.2, 20.3, 20.0, 16.9, 16.8, 12.8. IR (NaCl/thin film): 2948, 2867, 2033, 1741, cm$^{-1}$; HRMS (ES+) calc'd for $C_{18}H_{26}O_3Si$ $[M+H]^+$ 319.1724, found 319.1719.

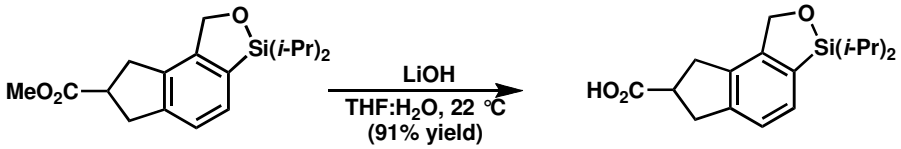
**Preparation of Ester 24**




23 24

A flame-dried 250 mL three-neck round bottom flask, equipped with condenser and magnetic stir bar, was charged with a degassed (3 freeze-pump-thaw cycles) solution of triyne **23** (4.00 g, 12.6 mmol) in dichloroethane (40 mL). A solution of RuCp*(cod)Cl (55.0 mg, 144 μmol) in DCE (10 mL) was prepared in a glove-box and slowly added to the triyne solution at 22 °C. **Warning**: Reaction is highly exothermic. Use of chilled (0 °C) water condenser is required. Upon completion of the catalyst addition the reaction was heated at 50 °C for 30 min. After cooling to 22 °C the solution was concentrated under reduced pressure, crude oil was purified by flash chromatography (0→15% EtOAc/hexanes) to afford **24** (3.61 g, 90% yield) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, $J$ = 7.3 Hz, 1H), 7.18 (d, $J$ = 7.3 Hz, 1H), 5.11 – 4.92 (m, 2H), 3.74 (s, 3H), 3.39 (quintet, $J$ = 8.6 Hz, 1H), 3.35 – 3.18 (m, 2H), 3.18 – 2.98 (m, 2H), 1.29 – 1.13 (m, 2H), 1.13 – 0.90 (m, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.7, 146.6, 143.5, 134.6, 130.6, 129.7, 123.0, 71.1, 52.0, 43.1, 36.1, 33.9, 17.0, 17.0, 13.1, 13.1. IR (NaCl/thin film): 2944, 2864, 1738 cm$^{-1}$; HRMS (ES+) calc'd for $C_{18}H_{27}O_3Si$ $[M+H]^+$ 319.1729, found 319.1717.

**Preparation of Acid S8**

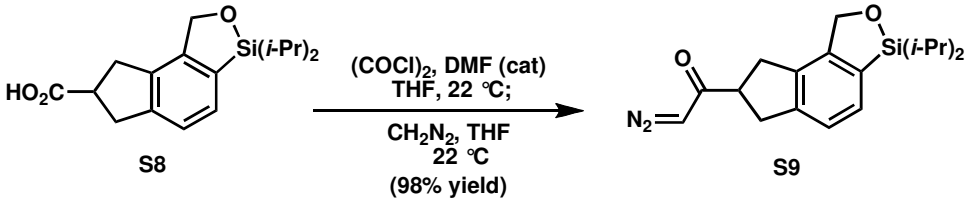



24 S8

To a solution of ester **24** (1.70 g, 5.34 mmol) in THF (40 mL) at 22 °C was added solution of LiOH (0.26 g, 11 mmol) in $H_2O$ (20 mL). The resulting heterogeneous mixture was stirred vigorously for 60 min, after which time the reaction became homogeneous. TLC analysis indicated consumption of starting material. The reaction was diluted with $CH_2Cl_2$ (250 mL) and washed with aqueous 1M HCl (ca. 100 mL), saturated aqueous NaCl (ca. 100 mL), dried over

anhydrous $MgSO_4$, filtered and concentrated under reduced pressure afford acid **S8** (1.59 g, 98% yield) as a yellow oil which was used without further purification. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 5.09 – 4.99 (m, 2H), 3.44 (tt, *J* = 9.3, 8.0 Hz 1H), 3.38 – 3.26 (m, 2H), 3.21 – 3.06 (m, 2H), 1.24 – 1.14 (m, 2H), 1.01 (m, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 181.1, 146.5, 143.30, 134.4, 130.7, 129.8, 123.0, 71.1, 43.0, 36.0, 33.7, 17.0, 13.1, 13.1. IR (NaCl/thin film): 3023, 2944, 2864, 1734, 1707 cm$^{-1}$. HRMS (ES+) calc'd for $C_{17}H_{23}O_3Si$ $[M - H]^-$ 303.1422, found 303.1427.

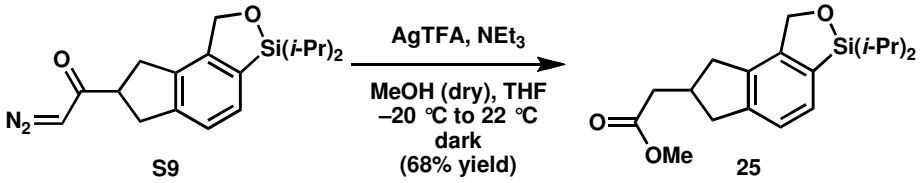
**Preparation of Diazo Ketone S9**




A flame-dried 25 mL flask containing acid **S8** (131 mg, 0.430 mmol) was charged with THF (5 mL) under $N_2$. To the resulting solution was added 1 drop of DMF, followed by oxalyl chloride (73 μL, 0.86 mmol) at 22 °C. Within 10 min gas evolution stopped and solvent was removed under the reduced pressure, followed by azeotroping with 3 x 10 mL anhydrous benzene to remove traces of residual HCl. $^1$H NMR analysis confirmed clean conversion of the starting acid **S8** to the acid chloride. The resulting yellow oil was diluted with THF (10 mL) under $N_2$. Diazomethane (~5-6 mmol, solution in $Et_2O$) was briefly dried over KOH (5 min) and carefully decanted at 0 °C into a 50 mL Erlenmeyer flask. The acid chloride/THF solution was then transferred via Teflon cannula to excess diazomethane at 0 °C with gentle stirring, resulting in steady gas evolution. The solution was warmed to 22 °C over the period of 10 h. TLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure (with AcOH in the trap to quench any unreacted $CH_2N_2$). The crude yellow oil was purified by flash chromatography (4:1 EtOAc/hexanes), yielding diazo ketone **S9** (130 mg, 98% yield) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 5.32 (br. s, 1H), 5.12 – 4.92 (m, 2H), 3.37 (br. s, 1H), 3.28 (dd, *J* = 16.1, 7.7 Hz, 1H), 3.20 (dd, *J* = 16.0, 9.2 Hz, 1H), 3.10 (dd, *J* = 15.7, 7.6 Hz, 1H), 3.00 (dd, *J* = 15.8, 9.0 Hz, 1H), 1.32 – 1.13 (m, 2H), 1.03-0.97 (m, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 196.2, 146.6, 143.4, 134.5, 130.7, 129.8, 123.0, 71.2, 54.0, 49.1, 36.0, 33.8, 17.0, 13.10, 13.08.

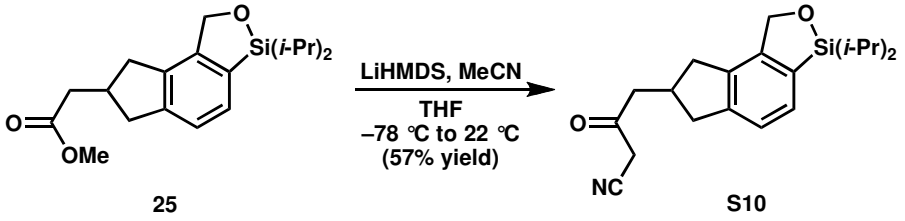
IR (NaCl/thin film): 2942, 2863, 2104, 1641 $cm^{-1}$. HRMS (ES+) calc'd for $C_{18}H_{25}N_2O_2Si$ $[M+H]^+$ 329.1685, found 329.1676.

**Preparation of Methyl Ester 25**




A 25 mL flame-dried flask was charged with diazo ketone **S9** (87 mg, 0.27 mmol). Dry benzene (10 mL) was added and evaporated under vacuum. The azeotropic procedure was repeated two additional times. Theresulting material was dried under high vacuum for 30 min then dissolved in THF (3 mL) and dry MeOH (300 μL) was added. The flask was covered in foil and cooled to –20 °C. A solution of silver trifluoroacetate (6.0 mg, 0.03 mmol) in $Et_3N$ (110 μL, 0.80 mmol) was added in one portion to the diazo ketone solution at –20 °C. (Note: vigorous stirring during $Et_3N$ addition is critical to ensure dissolution of silver salt. Lack of stirring can result in a brown silver clump and incomplete dissolution. When dissolved one obtains a clear tan solution). The reaction was slowly warmed over 4 h to 22 °C (starting material consumption was confirmed by TLC). The reaction was diluted with diethylether (15 mL) quenched with 1M HCl (2 mL). The aqueous layer was extracted with 20 mL $Et_2O$, and the combined organics were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude brown oil was purified by flash chromatography (8:1 EtOAc/hexanes), yielding ester **25** (60 mg, 68% yield) as a clear oil. $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.36 (d, $J$ = 7.3 Hz, 1H), 7.16 (d, $J$ = 7.3 Hz, 1H), 5.14 – 4.89 (m, 2H), 3.70 (s, 3H), 3.18 (dd, $J$ = 15.9, 7.9 Hz, 1H), 3.01 (dd, $J$ = 15.5, 8.0 Hz, 1H), 2.98 – 2.88 (m, 1H), 2.68 (dd, $J$ = 15.9, 7.4 Hz, 1H), 2.58 – 2.49 (m, 2H), 2.50 (dd, $J$ = 15.9, 6.9 Hz, 1H), 1.35 – 1.11 (m, 2H), 1.11 – 0.82 (m, 12H); IR (NaCl/thin film): 2943, 2864, 1739 $cm^{-1}$; HRMS (ES+) calc'd for $C_{19}H_{29}O_3Si$ $[M+H]^+$ 333.1886, found 333.1875.

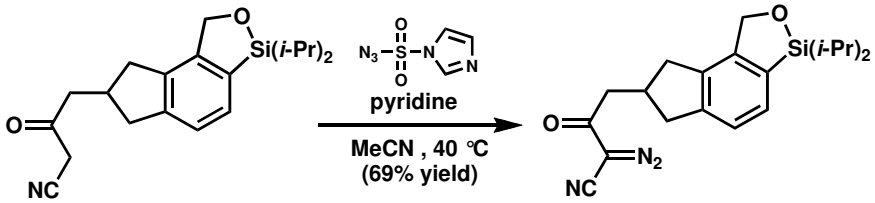
**Preparation of β-Ketonitrile S10**




25 S10

A flame-dried 25 mL flask was charged with LiHMDS (1M solution in THF, 780 μL, 0.78 mmol) and THF (2 mL), and cooled to –78 °C. MeCN (48 μL, 0.90 mmol) was added dropwise and solution was stirred at –78 °C for 30 min. Ester **25** (120 mg, 0.36 mmol) in THF (3 mL) was added dropwise and resulting solution was left at –78 °C for 60 min then warmed to 22 °C. TLC analysis showed complete consumption of starting material. $Et_2O$ (50 mL) was added and the reaction was quenched by the addition of aqueous saturated $NH_4Cl$ (ca. 20 mL). The organic layer dried $MgSO_4$ and concentrated under reduced pressure. The crude yellow oil was purified by flash chromatography (0→40% EtOAc/hexanes) to yield β-ketonitrile **S10 (**105 mg, 90% yield) as a colorless oil. NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 5.10 – 4.86 (m, 2H), 3.48 (s, 2H), 3.22 (dd, *J* = 15.9, 7.9 Hz, 1H), 3.05 (dd, *J* = 13.7, 6.1 Hz, 1H), 3.04 – 2.92 (m, 1H), 2.92 – 2.80 (m, 2H), 2.62 (dd, *J* = 15.9, 7.1 Hz, 1H), 2.43 (dd, *J* = 15.5, 6.7 Hz, 1H), 1.30 – 1.11 (m, 2H), 1.12 – 0.77 (m, 12H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 196.8, 146.7, 144.0, 135.1, 130.4, 129.6, 123.1, 113.6, 71.2, 48.0, 38.7, 36.4, 34.2, 32.2, 17.00, 16.99, 16.97, 13.1. IR (NaCl/thin film): 2943, 2864, 2261, 1732 $cm^{-1}$; HRMS (ES+) calc'd for $C_{20}H_{28}NO_2Si$ $[M+H]^+$ 342.1889, found 342.1881.

**Preparation of Diazo β-Ketonitrile 26**

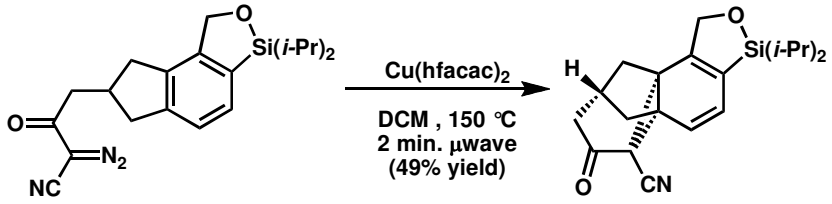



S10 26

Pyridine (120 mL, 1.5 mmol) was added to a solution of imidazole-1-sulfonyl azide (61 mg, 0.35 mmol) and β-ketonitrile **S10** (100 mg, 0.29 mmol) in MeCN (6 mL). Reaction mixture was stirred at 40 °C for 12 h, after which time TLC analysis confirmed consumption of the starting β-ketonitrile **S10**. The solvent was removed under reduced pressure and crude residue was purified by flash chromatography (0→20% EtOAc/hexanes), yielding α-diazo-α-ketonitrile

**26** (85 mg, 79% yield) as a yellow oil. NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 5.15 – 4.86 (m, 2H), 3.21 (dd, *J* = 15.8, 8.0 Hz, 1H), 3.12 – 2.93 (m, 2H), 2.93 – 2.76 (m, 2H), 2.69 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.60 – 2.41 (m, 1H), 1.28 – 1.15 (m, 2H), 1.04 – 0.96 (m, 12H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 189.4, 146.7, 144.0, 135.1, 130.5, 129.6, 123.1, 108.4, 71.2, 57.5, 45.1, 38.8, 36.4, 35.3, 17.0, 13.1); IR (NaCl/thin film): 2942, 2864, 2222, 2128, 1678$cm^{-1}$; HRMS (ES+) calc'd for $C_{20}H_{26}NO_2Si$ $[M–N_2+H]^+$ 340.1738, found 340.1718.

**Cyclopropanation of α-Diazo-β-Ketonitrile 26**




**26** **27**

A 5 mL microwave vial equipped with a stir bar was charged with α-diazo-β-ketonitrile **26** (10.0 mg, 0.027 mmol) in $CH_2Cl_2$ (2 mL). $Cu(hfacac)_2$ (1.3 mg, 0.03 mmol) in $CH_2Cl_2$ (0.7 mL) was added via syringe through the septa of the sealed vial. The vial was placed into the microwave reactor and heated to 150 °C for 2 min (ramp from 22 °C to 120 °C required 2 min). TLC analysis confirmed consumption of the starting material. The solvent was concentrated under reduced pressure, and the crude residue was purified by flash chromatography (1:3 EtOAc/hexanes), yielding norcaradiene **27** (4.5 mg, 49% yield) as a white solid. $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.52 (d, *J* = 9.1 Hz, 1H), 6.18 (dd, *J* = 9.2, 0.9 Hz, 1H), 4.91 (dd, *J* = 16.6, 0.6 Hz, 1H), 4.72 (d, *J* = 16.6 Hz, 1H), 2.55 – 2.36 (m, 1H), 2.36 – 2.28 (m, 2H), 2.19 (d, *J* = 3.0 Hz, 2H), 2.17 (d, *J* = 5.2 Hz, 1H), 2.10 (d, *J* = 12.7 Hz, 1H), 1.23 – 1.07 (m, 2H), 1.06 –1.00 (m, 12H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 199.3, 149.1, 128.9, 128.1, 122.1, 111.9, 72.6, 51.0, 48.3, 43.4, 36.0, 34.5, 30.0, 26.1, 17.04, 16.98, 16.7, 16.6, 13.0, 12.9. IR (NaCl/thin film): 2943, 2864, 2239, 2128, 1699 $cm^{-1}$; HRMS (ES+) calc'd for $C_{20}H_{26}NO_2Si$ $[M +H]^+$ 340.1733, found 340.1720.

**Catalyst Screen: General Procedure for Diazoketone 14 (Table 1).**

**Method A**: A sealed 1 mL vial equipped with a stir bar was flushed with $N_2$ and charged with a stock solution of diazo **14** (0.005 mmol) and mesitylene (0.005 mmol)[9] in $CD_2Cl_2$ (400 μL), followed by the rhodium catalyst (0.0005 mmol) in $CD_2Cl_2$ (100 μL). The solution was stirred for 12 hours under nitrogen. TLC analysis confirmed consumption of the starting material. The solution was transferred to an NMR tube and the yield of cyclopropane **18** was determined relative to the ratio of **14**:mesitylene in the stock solution.[10]

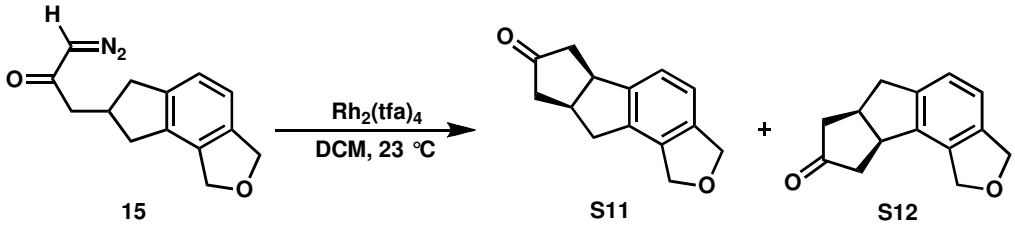
**Method B**: A sealed 0.5 mL microwave vial equipped with a stir bar was flushed with $N_2$ and charged with a stock solution of the diazo compound (0.005 mmol) and mesitylene (0.005 mmol)[9] in $CD_2Cl_2$ (400 μL), followed by the copper catalyst (0.0005 mmol) in $CD_2Cl_2$ (100 μL). The solution was heated in a Biotage Initiator microwave reactor at 100 °C for 1 min (ramp from 22 °C to 100 °C required 2 min). TLC analysis confirmed consumption of the starting material. The solution was transferred to a NMR tube and the yield of cyclopropane **18** was determined relative to the ratio of **14**:mesitylene in the stock solution.[10]

**Catalyst Screen: General Procedure for the Diazo Substrates 16 and 17 (Table 2).**

A sealed 0.5 mL microwave vial equipped with a stir bar was flushed with $N_2$ and charged with a solution of diazo-compound (0.005 mmol) and mesitylene (ca. 0.005 mmol)[9] in $CD_2Cl_2$ (400 μL), followed by a solution of the copper catalyst (0.0005 mmol) in $CD_2Cl_2$ (100 μL). The solution was heated in a Biotage Initiator microwave reactor at 120 °C for 1 minute (ramp from 22 °C to 120 °C required 2 min). The solution was transferred to a NMR tube and the yield of cyclopropane product was determined relative to the ratio of diazo:mesitylene in the stock solution.[10]

(9) The exact ratio of diazo compound to internal standard (mesitylene) in the stock solution was assessed by $^1H$ NMR analysis.
(10) A 15 second delay time (D1) was employed for all NMR measurements.

**Isolation of C-H Insertion of Byproducts of α-Diazoketone 14**




A flame-dried 50 mL round bottom flask, equipped with stir bar and septa, was charged with $Rh_2(tfa)_4$ (2 mg, 0.003 mmol) and DCM (10 mL). A solution of **14** (15 mg, 0.06 mmol) in DCM (2 mL) was slowly added to the above solution at over the period of 5 minutes. Gas evolution was observed. The resulting solution was stirred for an additional 2 hours. TLC analysis confirmed consumption of the starting diazoketone **14**, and reaction mixture was concentrated under reduced pressure. $^1$H NMR analysis of the crude reaction mixture indicated approximately 40% combined yield of two isomeric C-H insertion products (~8:1 ratio of C-H insertion to cyclopropanation). The crude residue was loaded on preparative TLC plate and developed in 1:1 EtOAc/hexanes. UV active band with Rf ~ 0.6 was cut out and extracted into EtOAc. Further purification was achieved by preparative HPLC chromatography (20% EtOAc/hexanes), yielding two C-H insertion products (±)-**S11** (2 mg, 7% yield) and (±)-**S12** (1.5 mg, 5% yield) as white solids. Relative stereochemistry was assigned by NOE experiments.

**S11** (less polar product): $^1$H NMR (600 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 5.08 (s, 2H), 5.03 (d, *J* = 12.1 Hz, 1H), 3.93 – 3.79 (m, 1H), 3.30 – 3.17 (m, 2H), 2.84 (app. d, *J* = 13.7 Hz, 1H), 2.65 (ddd, *J* = 19.0, 9.6, 1.6 Hz, 1H), 2.58 (ddd, *J* = 18.9, 8.8, 1.3 Hz, 1H), 2.41 (ddd, *J* = 18.9, 3.8, 1.1 Hz, 1H), 2.08 (ddd, *J* = 18.8, 7.3, 1.2 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 218.6, 141.8, 138.5, 138.2, 135.7, 124.4, 119.9, 73.3, 71.8, 44.9, 43.9, 41.8, 39.7, 38.5. IR (NaCl/thin film): 2916, 2849, 1731, 1462 cm$^{-1}$; HRMS (ES+) calc'd for $C_{14}H_{13}O_2^+$ $[M - H]^+$ 213.0910, found 213.0914.

**S12** (more polar product): $^1$H NMR (600 MHz, $CDC_3$) δ 7.10 (s, 2H), 5.13 – 5.08 (m, 2H), 5.05 (s, 2H), 3.88 (td, *J* = 7.3, 1.9 Hz, 2H), 3.24 (pd, *J* = 7.2, 1.9 Hz, 1H), 3.15 (dd, *J* = 16.1, 7.4 Hz, 1H), 2.73 (ddd, *J* = 19.0, 9.4, 1.7 Hz, 1H), 2.68 (d, *J* = 1.9 Hz, 1H), 2.59 – 2.54 (m, 2H), 1.97 (dd, *J* = 18.9, 8.4 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 218.8, 144.6, 138.4, 136.0, 123.6, 119.6, 73.6, 72.5, 65.9, 45.6, 43.9, 43.6, 39.8, 36.9. IR (NaCl/thin film): 2917, 2849, 1737, 1465 cm$^{-1}$; HRMS (ES+) calc'd for $C_{14}H_{13}O_2^+$ $[M - H]^+$ 213.0910, found 213.0913.